Treatment of Wilson's Disease for Patients in the United Kingdom

Introduction

Copper is a small but essential part of our daily diet. In patients with Wilson's disease, the route of excretion of dietary copper is impaired and this results in an overload of copper in the body. The signs and symptoms of Wilson's disease are the consequence of this copper overload affecting various organs such as the liver and the brain. Wilson's disease can be treated by reducing the copper overload with the use of appropriate medication.

Drugs approved in the UK for Wilson's disease and how they work – March 2021

Currently, four drugs are approved for use in the UK for treating Wilson's disease: **D-penicillamine**, **trientine** in the form of **trientine dihydrochloride** or **trientine tetrahydrochloride**, and **zinc acetate dihydrate**. All four drugs are taken orally. D-Penicillamine and the two trientine formulations are "chelating agents", which attach to the copper in the body and remove it by urinary excretion. Zinc acetate dihydrate has a different mode of action and is known as an "inhibiting agent". It essentially limits the intestinal absorption of dietary copper, which leads to an overall decrease in copper overload in the body.

Taking the medication regularly

For patients newly diagnosed with Wilson's disease, the initial choice of one of these four drugs and the number of capsules or tablets to be taken each day will be determined by their consultant. **In order to reduce copper overload, it is very important for patients to take their prescribed medication regularly, and at recommended times during the day. Treatment is lifelong.** Taking the medication on an empty stomach will enhance the amount of these drugs which is absorbed by the body. Patients will be given advice about the best way to take their medication between meals.

Brand names

Trientine and penicillamine are the generic (INN) names for these two drugs, while zinc acetate dihydrate is the accepted chemical name for this substance. But in addition, brand names are also used to identify penicillamine, the two trientine formulations and zinc acetate. In the UK, one of the brand names for penicillamine is **Distamine**, for trientine dihydrochloride (sold by Univar Solutions) it is **Cufence**, and for trientine tetrahydrochloride (sold by Orphalan UK) it is **Cuprior**. Zinc acetate has the brand name **Wilzin** and is marketed by Recordati Rare Diseases UK.

Package leaflets

Brand names are used to identify the drugs used to treat Wilson's disease in **Package leaflets: information for the patient**. These leaflets are always included with a prescribed medicine and provide much useful information such as recommended doses, possible adverse effects, dietary advice and how to store the medication. There are five weblinks to **package leaflets** for the drugs currently approved to treat Wilson's disease patients in the UK:

Penicillamine: pil.4069.pdf (medicines.org.uk)

Trientine dihydrochloride (Cufence): Cufence II-02 e ma-combined-h-4111-en-clean (medicines.org.uk)

Trientine dihydrochloride (available from Tillomed Laboratories Ltd. UK): https://www.medicines.org.uk/emc/files/pil.11626.pdf

Trientine tetrahydrochloride (Cuprior): ema-combined-h4005_en_annotated (medicines.org.uk)

Zinc acetate (Wilzin): Wilzin, INN-zinc acetate dihydrate (medicines.org.uk)

Liver transplantation

Liver transplantation is needed for Wilson's disease patients with acute liver failure at initial presentation or end-stage liver failure as a result of discontinued or unsuccessful drug therapy. The conundrums and outcomes of liver transplants in Wilson's disease have been summarised (Michelle Camarata *et al*, 'General considerations and the need for liver transplantation'. In, *Wilson Disease: Pathogenesis. Molecular Mechanisms, Diagnosis, Treatment and Monitoring*, edited by Karl Heinz Weiss and Michael Schilsky, Academic Press, London, 2019, chapter 15, pp 173-182; https://doi.org/10.1016/B978-0-12-811077-5.00015-3).

Future treatments for Wilson's disease

A new drug: bis(choline) tetrathiomolybdate

Clinical trials of promising research into diseases are recorded on the website Home - ClinicalTrials.gov, hosted by the US National Library of Medicine. At present (March 2021), thirty-three clinical trials on Wilson's disease are listed on this site. As well as trials into new ways of administering and assessing existing drugs for Wilson's disease (trientine and zinc formulations), the website shows that there are nine studies currently planned, underway or completed of a new copper–protein binding agent, **bis(choline) tetrathiomolybdate**, code name ALXN1840 (previous code name WTX 101). Regulatory approval for the use of bis(choline) tetrathiomolybdate in patients with Wilson's disease has yet to be given in the UK.

A cure for Wilson's disease is on the horizon

Gene therapy offers the prospect of a cure for the genetic defect responsible for the copper overload in patients with Wilson's disease, thus removing the need for drug therapy. The ClinicalTrials.gov website gives details of a Phase I/II study of a gene therapy product (VTX-801), which was due to have started in February 2021 with Wilson's disease patients.

Dietary Copper

All agricultural soils contain copper (about 30 mg/kg in the UK). Therefore, copper is naturally present in the diet and some precautions about which foods should possibly be avoided (or eaten in moderation) may be necessary for patients with Wilson's disease. Along with regular medication, awareness of the amounts of copper in different foods is a sensible strategy. A list of copper values in common foods eaten in the United Kingdom may be found in the *Diet* section WDSG-UK :: Diet and Copper Content of Foods (wilsonsdisease.org.uk).

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